AF IFW 1635

Attorney Docket No. P66141US0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: SCHLINGENSIEPEN et al.

Serial No.: 09/701,583 Art Unit: 1635

Filed: February 5, 2001 Examiner: Jane J. Zara

For: A METHOD FOR STIMULATING THE IMMUNE SYSTEM

PETITION UNDER 37 CFR 1.144

Attn: Director – Technology Center 1635
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Petitioners request review of the final restriction requirement mailed December 6, 2006, vacating of the restriction, and instructions that any future restriction, and examination, be consistent with Manual of Patent Examining Procedure (MPEP) 803.04 (copy attached), as detailed below.

No fee is necessary in connection with the instant petition. Should any fee be required charge the fee to Deposit Account No. 06-1358 and, should the petition be granted, credit refund of the fee to Deposit Account No. 06-1358.

Facts

Currently, independent claim 1 and dependent claims 2-11 are pending. Claim 1 (as presently amended) reads:

1. A composition comprising a physiologically acceptable combination of:
   - at least one inhibitor of the effect of a substance negatively effecting an immune response, wherein the inhibitor is an oligonucleotide having a sequence according to one of SEQ ID NOS: 1-213, unmodified or having one

or more modifications selected from the group consisting of phosphorothioate internucleotide linkages, methylphosphonate internucleotide linkages, phosphoramidate linkages, peptide linkages, 2'-O-modified sugar, and modified bases and

- at least one stimulator positively effecting an immune response.

Pursuant to the final restriction requirement, examination of claims 1-11 was limited to SEQ ID NOS: 7, 9, and 14 and subject matter corresponding to SEQ ID NOS: 1-6, 8, 10-13, and 15-213 was withdrawn from consideration.

The initial restriction applied to claim 10, reciting specific antisense nucleotide sequences, under 35 USC 121 (Office Action mailed February 5, 2004, copy attached: the "1st written restriction"). According to the 1st written restriction (page 3).

> Pursuant to 35 U.S.C. 121 and 37 C.F.R. 1.141, the nucleotide sequences listed in claim 10 are subject to restriction. As per M.P.E.P. 2434, "the Commissioner has partially waived the requirements of 37 C.F.R. 1.141 and will permit a reasonable number of such nucleotide or amino acid sequences to be claimed in a single application." Under this policy, in most cases, up to 1 (one) independent and distinct nucleotide OR amino acid sequence will be examined in a single application without restriction. Those sequences which are patentably indistinct from the sequence selected by the applicant will also be examined.
>
> Claim 10 specifically claims nucleotide sequences encoding antisense targeting various target nucleic acids, and these individual SEQ ID Nos. are listed in claim 10. Each of these antisense sequences is considered to be structurally independent, because each of these sequences has a unique nucleotide sequence, and each targets a specific region of a particular gene or a specific target gene. Furthermore, a search of all the sequences claimed presents an undue burden on the Patent and Trademark Office to search and examine all of the recited sequences. In view of the foregoing, applicants are required to elect up to 1 claimed nucleotide sequence from the claim.

Pursuant to the restriction requirement petitioners elected to prosecute nucleotide SEQ ID NO: 7, with traverse (Response filed May 5, 2004, copy attached).

By subsequent amendment (filed October 4, 2005, copy attached) claim 1 was limited, *i.a.*, to "SEQ ID NOS: 1-213." A second restriction was then made (mailed January 4, 2006, copy attached) (the "second written restriction") stating (emphasis in original):

> Please elect two additional nucleotide sequences (in addition to the elected SEQ ID NO: 7) from claims 1 and 10, for the reasons set forth below:
>
> Pursuant to 35 U.S.C. 121 and 36 C.F.R. 1.141, the nucleotide sequences listed in claims 1 and 10 are subject to restriction. As per M.P.E.P. 2434, "the Commissioner has partially waived the requirements of 37 C.F.R. 1.141 and will permit a reasonable number of such nucleotide or amino acid sequences to be claimed in a single application." Those sequences which are patentably indistinct from the sequence(s) selected by the applicant will also be examined.
>
> Claims 1 and 10 specifically claim nucleotide sequences encoding antisense oligonucleotides targeting various target nucleic acids, and these individual SEQ ID Nos. are listed in claims 1 and 10. Each of these antisense sequences is considered to be structurally independent, because each of these sequences has a unique nucleotide sequence, and each targets a specific region of a particular gene or a specific target gene. A search of all the sequences claimed presents an undue burden on the Patent and Trademark Office to search and examine all of the recited sequences. In view of the foregoing, applicants are required to elect up to two more nucleotide sequences (in addition to the previously presented elected SEQ ID NO: 7) from claims 1 and 10.

SEQ ID NOS: 9 and 14 were elected, with traverse, in response to the second written restriction (response filed January 31, 2006, copy attached). The second written restriction was confirmed (made final) in the Office Action mailed April 21, 2006 (copy attached), reconsideration of the final, second written restriction was requested (filed September 21, 2006, copy attached), and the request for reconsideration was denied (Office Action mailed December 6, 2006, copy attached). In denying

the request for reconsideration, the examiner stated (Office Action mailed December 6, 2006, pages 2-3) (emphasis in original):

> Applicant's election with traverse of SEQ ID Nos. 7, 9 and 14 in the replies filed on January 31, 2006 and September 21, 2006 is acknowledged. The traversal is on the ground(s) that the requisite number of sequences examined in an application as set forth in the MPEP at 803.04 is ten. This is not found persuasive because the MPEP at 803.04 set forth the suggested maximum number of sequences to be searched in a single application to be ten. It did not set forth a requisite number of sequences to be searched in a single application. Furthermore, at the time these suggested guidelines for restrictions were written, the data bases were not as extensive and so sequence searches were much less burdensome to perform, and so ten was often a reasonable amount of sequences to search. Since then, the data bases that must be searched for adequate examination of sequences have expanded tremendously (e.g. data continues to stream in from the various genome projects). For these reasons, the restriction to three sequences is a reasonable number and, hence, the instant restriction requirement is proper.
>
> The requirement is still deemed proper and is therefore made FINAL.
>
> Claim 6 and SEQ ID Nos. other than SEQ ID Nos. 7, 9 and 14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on September 21, 2006.

Points of Review

The restriction improperly (1) limited election to only one nucleotide sequence, instead of 10 nucleotide sequences [MPEP 803.04/2434], and (2) limited examination to only the one elected sequence (SEQ ID NO: 7) together with only 2 patentably indistinct sequences (SEQ ID NOS: 9 and 14), instead of together with all of SEQ ID NOS: 1-32 and 58-67, as antisense oligonucleotides corresponding to a single gene encoding a single protein [MPEP 803.04/2434].

1. Election of 10 Nucleotide Sequences Must Be Permitted

According to MPEP 803.04 ("Nucleotide Sequences") (emphasis added)

> to further aid the biotechnology industry in protecting its intellectual property without creating an undue burden on the Office, the Director has decided sua sponte to . . . permit a reasonable number of such nucleotide sequences to be claimed in a single application. . . . It has been determined that normally ten sequences constitute a reasonable number for examination purposes. . . . Applications claiming more than ten individual independent and distinct nucleotide sequences in alternative form . . . will be subject to a restriction requirement [allowing for] ten nucleotide sequences selected in response.

Similarly, according to MPEP 2434 ("Examination of Patent Applications Claiming Large Numbers of Nucleotide Sequences") (copy attached),

> in most cases, up to 10 independent and distinct nucleotide sequences will be examined in a single application without restriction.

The examiner mistakenly relied on MPEP 2434 in making the restriction, with all due respect, in permitting only 1—instead of 10—as the number of sequences petitioners could elect. As stated by the examiner (1st written restriction, page 3) under MPEP 2434

> in most cases, up to 1 (one) independent and distinct nucleotide sequence OR amino acid sequence will be examined in a single application without restriction.

Contrary to the requirements of MPEP 803.04—and MPEP 2434— the examiner erroneously required selection of a single nucleotide sequence, rather than the requisite "ten nucleotide sequences."

Moreover, contrary to one of the aforesaid statements made in the written restriction, the Patent and Trademark Office determined that "ten sequences" can be examined "without creating an undue burden on the Office." MPEP 803.04 (emphasis added).

On the other hand, however, restricting examination to a single nucleotide does, most certainly, place an undue burden on petitioners. Requiring petitioners to file a divisional application for every, single nucleotide sequence would be an undue cost burden, at the very least.

The examiner maintains that petitioners are not entitled to examination of ten nucleotide sequences, but only "up to" ten sequences. It is true MPEP 2434 states "up to ten independent and distinct nucleotide sequences will be examined in a single application without restriction." However, MPEP 2434 also makes it clear that only in

> exceptional cases, the complex nature of the claimed material may necessitate that the reasonable number of sequences to be selected be less than ten.

There is no apparent "complex nature of the claimed material"—nor does the examiner argue differently—that would "necessitate that the reasonable number of sequences to be selected [in the present case] be less than ten." MPEP 2434.

Moreover, the restriction requirement to "1" nucleotide sequence does not even meet the "up to 10" standard set in the MPEP, as maintained by the examiner. Such an interpretation would render MPEP 803.04 and 2434 ineffectual. In other words, "the Commissioner" cannot have "partially waived" the rules limiting examination to a single sequence if the examiner can still require restriction to a single nucleotide sequence.

2. SEQ ID NOS: 1-32 and 58-67 Must Be Examined Together

As pointed out in their response filed January 31, 2006, pursuant to MPEP 2434:

> Nucleotide sequences encoding the same protein are not considered to be independent and distinct and will continue to be examined together.

In the present case, SEQ ID NOS: 1-32 and 58-67—which include elected SEQ ID NO: 7—are antisense oligonucleotides corresponding to a single gene encoding a single protein, i.e., protein TGF-β. Since the restriction resulted in SEQ ID NOS: 1-32 not being "examined together"—with elected SEQ ID NO: 7—the restriction was improper. MPEP 2434.

The restriction violates MPEP 803.04 – "Nucleotide Sequences" for the same reason. That is, MPEP 803.04 also requires (emphasis added)

> nucleotide sequences encoding the same protein are not considered to be independent and distinct inventions and will continue to be examined together.

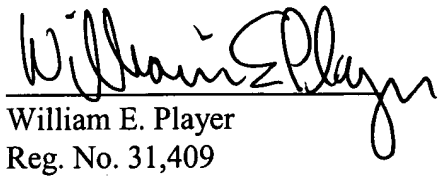
Action Requested

For the foregoing reasons, petitioners request (1) withdrawal of the restriction requirement and (2) the examiner be instructed to issue any future restriction requirement and, further, to examine the claims subsequent to response, thereto, consistent with MPEP 803.04, i.e., to allow election of ten nucleotide sequences in response to the restriction and, subsequently, to examine "the ten nucleotide sequences selected in response to the restriction requirement and any other claimed sequences which are patentably indistinct therefrom."

For the foregoing reasons, grant of the instant petition is in order and favorable action is requested.

Respectfully submitted,

JACOBSON HOLMAN PLLC

By 

William E. Player
Reg. No. 31,409

400 Seventh Street, NW
The Jenifer Building
Washington, D.C. 20004
Tel. (202) 638-6666
Fax (202) 393-5350
Date: March 13, 2007
WEP/jhr
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803.04 * Nucleotide Sequences [R-3]

By statute, "[i]f two or more independent and distinct inventions are claimed in one application, the *>Director< may require the application to be restricted to one of the inventions." 35 U.S.C. 121. Pursuant to this statute, the rules provide that "[i]f two or more independent and distinct inventions are claimed in a single application, the examiner in his action shall require the applicant . . . to elect that invention to which his claim shall be restricted." 37 CFR 1.142(a). See also 37 CFR 1.141(a).

>Polynucleotide molecules defined by their nucleic acid sequence (hereinafter "nucleotide sequences") that encode< different proteins are structurally distinct chemical compounds. These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such nucleotide sequence is presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141 *et seq*. Nevertheless, to further aid the biotechnology industry in protecting its intellectual property without creating an undue burden on the Office, the *>Director< has decided *sua sponte* to partially waive the requirements of 37 CFR 1.141 *et seq*. and permit a reasonable number of such nucleotide sequences to be claimed in a single application. See *Examination of Patent Applications Containing Nucleotide Sequences,* 1192 O.G. 68 (November 19, 1996).

It has been determined that normally ten sequences constitute a reasonable number for examination purposes. Accordingly, in most cases, up to ten independent and distinct nucleotide sequences will be examined in a single application without restriction. In addition to the specifically selected sequences, those sequences which are patentably indistinct from the selected sequences will also be examined. Furthermore, nucleotide sequences encoding the same protein are not considered to be independent and distinct inventions and will continue to be examined together.

In some exceptional cases, the complex nature of the claimed material, for example a protein amino acid sequence reciting three dimensional folds, may necessitate that the reasonable number of sequences to be selected be less than ten. In other cases, applicants may petition pursuant to 37 CFR 1.181 for examination of additional nucleotide sequences by providing evidence that the different nucleotide sequences do not cover independent and distinct inventions.

See MPEP § 1850 for treatment of claims containing independent and distinct nucleotide sequences in international applications filed under the Patent Cooperation Treaty (PCT) and national stage applications filed under 35 U.S.C. 371.

EXAMPLES OF NUCLEOTIDE SEQUENCE CLAIMS

Examples of typical nucleotide sequence claims impacted by the partial waiver of 37 CFR 1.141 *et seq*. (and the partial waiver of 37 CFR 1.475 and 1.499 *et seq*., see MPEP § 1850) include:

(A) an isolated and purified DNA fragment comprising DNA having at least 95% identity to a DNA sequence selected from SEQ ID Nos. 1-1,000;

(B) a combination of DNA fragments comprising SEQ ID Nos. 1-1,000; and

(C) a combination of DNA fragments, said combination containing at least thirty different DNA fragments selected from SEQ ID Nos. 1-1,000.

Applications claiming more than ten individual independent and distinct nucleotide sequences in alternative form, such as set forth in example (A), will be subject to a restriction requirement. Only the ten nucleotide sequences selected in response to the restriction requirement and any other claimed sequences which are patentably indistinct therefrom will be examined.

Applications claiming only a combination of nucleotide sequences, such as set forth in example (B), will generally not be subject to a restriction requirement. The presence of one novel and nonobvious sequence within the combination will render the entire combination allowable. The combination will be searched until one nucleotide sequence is found to be allowable. The order of searching will be chosen by the examiner to maximize the identification of an allowable sequence. If no individual nucleotide sequence is found to be allowable, the examiner will consider whether the combination of sequences taken as a whole renders the claim allowable.

Applications containing only composition claims reciting different combinations of individual nucleotide sequences, such as set forth in example

(C), will be subject to a restriction requirement. Applicants will be required to select one combination for examination. If the selected combination contains ten or fewer sequences, all of the sequences of the combination will be searched. If the selected combination contains more than ten sequences, the combination will be examined following the procedures set forth above for example (B). More specifically, the combination will be searched until one nucleotide sequence is found to be allowable with the examiner choosing the order of search to maximize the identification of an allowable sequence. The identification of any allowable sequence(s) will cause all combinations containing the allowed sequence(s) to be allowed.

In applications containing all three claims set forth in examples (A)-(C), the Office will require restriction of the application to ten sequences for initial examination purposes. Based upon the finding of allowable sequences, claims limited to the allowable sequences as in example (A), all combinations, such as in examples (B) and (C), containing the allowable sequences and any patentably indistinct sequences will be rejoined and allowed.

**>Nonelected claims< requiring any allowable >nucleotide< sequence(s) >should be considered for rejoinder. See MPEP § 821.04<. **

804 Definition of Double Patenting [R-5]

35 U.S.C. 101. Inventions Patentable.

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

35 U.S.C. 121. Divisional Applications.

If two or more independent and distinct inventions are claimed in one application, the Director may require the application to be restricted to one of the inventions. If the other invention is made the subject of a divisional application which complies with the requirements of section 120 of this title it shall be entitled to the benefit of the filing date of the original application. A patent issuing on an application with respect to which a requirement for restriction under this section has been made, or on an application filed as a result of such a requirement, shall not be used as a reference either in the Patent and Trademark Office or in the courts against a divisional application or against the original application or any patent issued on either of them, if the divisional application is filed before the issuance of the patent on the other application. If a divisional application is directed solely to subject matter described and claimed in the original application as filed, the Director may dispense with signing and execution by the inventor. The validity of a patent shall not be questioned for failure of the Director to require the application to be restricted to one invention.

The doctrine of double patenting seeks to prevent the unjustified extension of patent exclusivity beyond the term of a patent. The public policy behind this doctrine is that:

> The public should . . . be able to act on the assumption that upon the expiration of the patent it will be free to use not only the invention claimed in the patent but also modifications or variants which would have been obvious to those of ordinary skill in the art at the time the invention was made, taking into account the skill in the art and prior art other than the invention claimed in the issued patent.

In re Zickendraht, 319 F.2d 225, 232, 138 USPQ 22, 27 (CCPA 1963) (Rich, J., concurring). Double patenting results when the right to exclude granted by a first patent is unjustly extended by the grant of a later issued patent or patents. *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982).

Before consideration can be given to the issue of double patenting, two or more patents or applications must have at least one common inventor and/or be either commonly assigned/owned or non-commonly assigned/owned but subject to a joint research agreement as set forth in 35 U.S.C. 103(c)(2) and (3) pursuant to the CREATE Act (Pub. L. 108-453, 118 Stat. 3596 (2004)). Congress recognized that the amendment to 35 U.S.C. 103(c) would result in situations in which there would be double patenting rejections between applications not owned by the same party (see H.R. Rep. No. 108-425, at 5-6 (2003)). For purposes of a double patenting analysis, the application or patent and the subject matter disqualified under 35 U.S.C. 103(c) as amended by the CREATE Act will be treated as if commonly owned. See also MPEP § 804.03. Since the doctrine of double patenting seeks to avoid unjustly extending patent rights at the expense of the public, the focus of any double patenting analysis necessarily is on the claims in the multiple patents or patent applications involved in the analysis.

There are generally two types of double patenting rejections. One is the "same invention" type double patenting rejection based on 35 U.S.C. 101 which states in the singular that an inventor "may obtain a patent." The second is the "nonstatutory-type" double patenting rejection based on a judicially created

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Phe Val
```

2434 Examination of Patent Applications Claiming Large Numbers of Nucleotide Sequences

The U.S. Patent and Trademark Office published its policy for the examination of patent applications that claim large numbers of nucleotide sequences in the *Official Gazette*, 1192 O.G. 68 (November 19, 1996). Nucleotide sequences encoding different proteins are structurally distinct chemical compounds and are unrelated to one another. These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such nucleotide sequence is presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141. In establishing the new policy, the Commissioner has partially waived the requirements of 37 CFR 1.141 and will permit a reasonable number of such nucleotide sequences to be claimed in a single application. Under this policy, in most cases, up to 10 independent and distinct nucleotide sequences will be examined in a single application without restriction.Those sequences which are patentably indistinct from the sequences selected by the applicant will also be examined. Nucleotide sequences encoding the same protein are not considered to be independent and distinct and will continue to be examined together. In some exceptional cases, the complex nature of the claimed material may necessitate that the reasonable number of sequences to be selected be less than 10. In other cases, applicants may petition pursuant to 37 CFR 1.181 for examination of additional nucleotide sequences by providing evidence that the different nucleotide sequences do not cover independent and distinct inventions. For examples of typical nucleotide sequence claims and additional information on the search and examination procedures, see the above cited O.G. Notice. See also MPEP § 803.04.

2435 Publishing of Patents and Patent Application Publications with Lengthy Sequence Listings

Due to the high cost and limited usefulness of the printed paper or composed electronic image versions of nucleotide and/or amino acid sequences, if the "Sequence Listing" portion is lengthy (i.e., at least 600 Kb (about 300 typed pages)), it will no longer be printed with the paper and composed electronic image (page image) versions of patents and patent application publications. The "Sequence Listing" will only be published in electronic form and will be available on the USPTO sequence homepage (http://seqdata.uspto.gov) as an ASCII text file.

Neither the paper copies of patents and patent application publications that are in the search rooms nor those sold through the Office of Public Records, Certification Division, will include a sequence listing if the sequence listing is not included in the composed

DJC 2/9/04 WEP P66141/US0

TC 2-10-04

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/701,583	02/05/2001	Karl-Hermann Schlingensiepen	P66141US0	7033

136 7590 02/05/2004

JACOBSON HOLMAN PLLC
400 SEVENTH STREET N.W.
SUITE 600
WASHINGTON, DC 20004

EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 02/05/2004

JACOBSON HOLMAN PLLC
Response Due On Or Before
3 / 5 / 04
Month Day Year

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/701,583	SCHLINGENSIEPEN ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-13* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-13 are pending in the instant application.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-5, 7, 8, 11-13 drawn to a medicament comprising a nucleic acid inhibitor and a stimulator of an immune response in a method to treat neoplasms, classifiable in class 514, subclasses 1 and 44.

II. Claims 1, 2, 6-8, 11-13 drawn to a medicament comprising an antibody inhibitor and a stimulator of an immune response in a method to treat neoplasms, classifiable in class 514, subclasses 1 and 2.

III. Claims 1-5, 7, 8, 11-13 drawn to a medicament comprising a nucleic acid inhibitor and a stimulator of an immune response in a method to treat infectious diseases, classifiable in class 514, subclasses 1 and 44.

IV. Claims 1-5, 7, 8, 11-13 drawn to a medicament comprising a antibody inhibitor and a stimulator of an immune response in a method to treat infectious diseases, classifiable in class 514, subclasses 1 and 2.

V. Claim 9, drawn to a medicament comprising multiple inhibitors and a stimulator, classified in class 530 and 536, subclasses 387.1 and 24.5, respectively.

VI. Claims 10, 11, drawn to nucleic acid compositions, classified in class 536, subclass 24.5.

Please elect a single substance from claim 1.

Please elect a single stimulator from claim 8.

Please elect a single nucleotide sequence from claim 10, for the reasons set forth below:

Pursuant to 35 U.S.C. 121 and 37 C.F.R. 1.141, the nucleotide sequences listed in claim 10 are subject to restriction. As per M.P.E.P. 2434, "the Commissioner has partially waived the requirements of 37 C.F.R. 1.141 and will permit a reasonable number of such nucleotide or amino acid sequences to be claimed in a single application." Under this policy, in most cases, up to 1 (one) independent and distinct nucleotide OR amino acid sequence will be examined in a single application without restriction. Those sequences which are patentably indistinct from the sequence selected by the applicant will also be examined.

Claim 10 specifically claims nucleotide sequences encoding antisense targeting various target nucleic acids, and these individual SEQ ID Nos. are listed in claim 10. Each of these antisense sequences is considered to be structurally independent, because each of these sequences has a unique nucleotide sequence, and each targets a specific region of a particular gene or a specific target gene. Furthermore, a search of all the sequences claimed presents an undue burden on the Patent and Trademark Office to search and examine all of the recited sequences. In view of the foregoing, applicants are required to elect up to 1 claimed nucleotide sequence from the claim.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II and III and IV and V and VI are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions comprise compositions or compounds that are chemically, biologically, structurally and functionally distinct from each other and thus one does not render the other obvious. The nucleic acids are different and distinct from each other (Groups I, III, V, VI), and are different and distinct from the antibodies (Groups II, IV, V). The nucleic acids are not required to produce the antibodies or the other nucleic acids. Therefore, the inventions of the various groups are capable of supporting separate patents.

Inventions I and II and III and IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions comprise biologically and functionally different and distinct Groups and thus one does not render the other obvious. The methods of Groups I and II and III and IV comprise steps which are not required for or present in the methods of the other groups: administration of compositions comprising nucleic acid inhibitors which target different genes for treatment of neoplasia or infectious diseases (Groups I and III, respectively), administration of compositions comprising antibodies for treatment of neoplasia or infectious diseases (Groups II and IV, respectively). Thus, the operation, function and effects of these different methods are different and distinct from each other. Therefore,

the inventions of these different, distinct groups are capable of supporting separate patents.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ
January 30, 2004

SEAN McGARRY
PRIMARY EXAMINER
1635

mop 1/6/06
TC 1-9-06

WCP

P66141US0

UNITED STATES PATENT AND TRADEMARK OFFICE

RESTRICTION

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/701,583	02/05/2001	Karl-Hermann Schlingensiepen	P66141US0	7033

136 7590 01/04/2006

JACOBSON HOLMAN PLLC
400 SEVENTH STREET N.W.
SUITE 600
WASHINGTON, DC 20004

JACOBSON HOLMAN PLLC
Response Due On Or Before
2 / 4 / 06
Month Day Year

EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/04/2006

COPY

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/701,583	SCHLINGENSIEPEN ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 6-11* is/are pending in the application.

4a) Of the above claim(s) *6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1, 2, 7-11* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 10-4-05.

Claims 1, 2, 6-11 are pending in the instant application.

Election/Restriction

Pursuant to 37 C.F.R. 1.142(a), upon further consideration, an examiner's action on the merits of the amendments and arguments filed by applicant on 10-4-05 insofar as they pertain to the elected invention is hereby deferred until a second election has been made. (See MPEP 810.02 and 811)

Please elect two additional nucleotide sequences (in addition to the elected SEQ ID NO: 7) from claims 1 and 10, for the reasons set forth below:

Pursuant to 35 U.S.C. 121 and 37 C.F.R. 1.141, the nucleotide sequences listed in claims 1 and 10 are subject to restriction. As per M.P.E.P. 2434, "the Commissioner has partially waived the requirements of 37 C.F.R. 1.141 and will permit a reasonable number of such nucleotide or amino acid sequences to be claimed in a single application." Those sequences which are patentably indistinct from the sequence(s) selected by the applicant will also be examined.

Claims 1 and 10 specifically claim nucleotide sequences encoding antisense oligonucleotides targeting various target nucleic acids, and these individual SEQ ID Nos. are listed in claims 1 and 10. Each of these antisense sequences is considered to be structurally independent, because each of these sequences has a unique nucleotide sequence, and each targets a specific region of a particular gene or a specific target

gene. A search of all the sequences claimed presents an undue burden on the Patent and Trademark Office to search and examine all of the recited sequences. In view of the foregoing, applicants are required to elect up to two more nucleotide sequences (in addition to the previously elected SEQ ID NO: 7) from claims 1 and 10.

The inventions are distinct, each from the other because of the following reasons:

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Conclusion

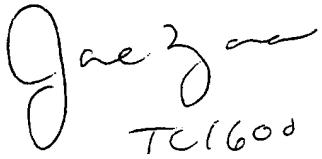
Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. 1.6(d)). The official fax telephone number for the

Group is **571-273-8300**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (571) 272-0811. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
12-23-05



mgt 12/8/04 DEP P66141US0

UNITED STATES PATENT AND TRADEMARK OFFICE

TC 12-11-06

FINAL REJECTION

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/701,583	02/05/2001	Karl-Hermann Schlingensiepen	P66141US0	7033

136 7590 12/06/2006

JACOBSON HOLMAN PLLC
400 SEVENTH STREET N.W.
SUITE 600
WASHINGTON, DC 20004

EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/06/2006

JACOBSON HOLMAN PLLC
Response Due On Or Before
3 16 07
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MAR 13 2007
IAP65
PATENT & TRADEMARK OFFICE

COPY

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	Application No.	Applicant(s)	
	09/701,583	SCHLINGENSIEPEN ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 6-11* is/are pending in the application.

4a) Of the above claim(s) *6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,7-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

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2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 9-21-06.

Claims 1, 2 and 6-11 are pending in the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

This application contains claim 6 and SEQ ID Nos. other than elected SEQ ID Nos.7, 9 and 14, drawn to an invention nonelected with traverse in the elections filed 1-31-06 and 9-21-06. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant's election with traverse of SEQ ID Nos. 7, 9 and 14 in the replies filed on 1-31-06 and 9-21-06 is acknowledged. The traversal is on the ground(s) that the requisite number of sequences examined in an application as set forth in the MPEP at 803.04 is ten. This is not found persuasive because the MPEP at 803.04 set forth the suggested maximum number of sequences to be searched in a single application to be ten. It did not set forth a requisite number of sequences to be searched in a single application. Furthermore, at the time these suggested guidelines for restrictions were written, the data bases were not as extensive and so sequence searches were much less burdensome to perform, and so ten was often a reasonable amount of sequences to search. Since then, the data bases that must be searched for adequate examination of sequences have expanded tremendously (e.g. data continues to stream in from the

various genome projects). For these reasons, the restriction to three sequences is a reasonable number and, hence, the instant restriction requirement is proper.

The requirement is still deemed proper and is therefore made FINAL.

Claim 6 and SEQ ID Nos. other than SEQ ID Nos.7, 9 and 14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 9-21-06.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 1, 2 and 7-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record set forth in the Office action mailed 4-21-06.

The claims are drawn to a composition comprising at least one oligonucleotide inhibitor of an immune response selected from SEQ ID Nos. 1-213, and further comprising at least one stimulator positively effecting an immune response, which stimulator optionally enhances the synthesis and/or function of factors selected from GM-CSF, SCF, CSF, IFN, FLT-3-ligand, monocyte chemotactic proteins, IL-2, IL-4, Il-12 and/or IL-18, a virus, viral antigen, tumor or pathogenic antigen, or organ specific

antigens expressed in affected organs but not essential for the organism or fusion of dendritic and tumor cells.

Applicant's arguments filed 9-21-06 have been fully considered but they are not persuasive. Applicant argues that adequate written description has been provided for the very broad genus comprising the above mentioned stimulators positively effecting an immune response because the term "medicament" has been removed from the claims and the instantly claimed invention does not embrace treatments. Applicants are correct that the claims have been amended and treatment effects are not inherently encompassed by the instant claims. However, contrary to Applicant's assertions, the removal of the term "medicament" from the instant claims does not satisfy the written description requirement for the very broad genus of biological agents claimed.

The genus claimed encompasses any stimulator of the immune response that enhances the synthesis or function of any molecule that stimulates, enhances, up-regulates or positively regulates the immune response, including but not limited to molecules or agents that lead to the stimulation or enhancement of the synthesis or function of *GM-CSF, SCF, CSF, IFN, FLT-3-ligands, monocyte chemotactic proteins, IL-2, IL-4, Il-12 and/or IL-18, any virus or viral antigens, any tumor or pathogenic antigens, and any organ specific antigens expressed in affected organs but not essential for the organism or fusion of dendritic and tumor cells.* The myriad of molecules embraced by this genus is vast (thousands and thousands of species). The laundry list of agents provided in the instant disclosure does not provide adequate support for the expansive

genus of biological agents claimed. For these reasons, the instant written description rejection is maintained.

Claims 1, 2, 7, 8, 10 and 11 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 12-15 of copending Application No. 10/984,919 for the reasons of record set forth in the Office action mailed 4-21-06.

No arguments have been made addressing this rejection.

Claims 1, 2, 7, 8, 10 and 11 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1 and 6 of copending Application No. 10/220,033 for the reasons of record set forth in the Office action mailed 4-21-06.

No arguments have been made addressing this rejection.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

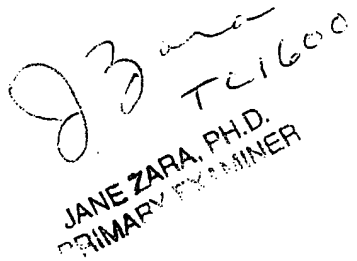
Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz, can be reached on (571) 272-0763. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
12-4-06



Attorney Docket No. P66141US0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: SCHLINGENSIEPEN et al.

Application No. 09/701,583 Group Art Unit: 1635

Filed: February 5, 2001 Examiner: J. ZARA

For: A METHOD FOR STIMULATING THE IMMUNE SYSTEM

RESPONSE
TO RESTRICTION REQUIREMENT

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Sir:

This paper responds to the Office Action (restriction requirement) mailed February 5, 2004.

Pursuant to the restriction requirement under 35 USC 121, election is made, hereby, to prosecute invention Group I, claims 1-5, 7, 8, 11-13, with traverse.

TGF-β is elected, with traverse, as the single substance from claim 1.

A tumor cell extract (specification page 5, species "m") is elected, with traverse, as the single stimulator from claim 8.

The oligonucleotide sequence TGF-β-123-2262 (No. 7) is elected, with traverse, as the oligonucleotide sequence from claim 10.

Applicant disagrees with the finding that inventions I to IV lack unity of invention. The invention, according to claim 1, is a medicament comprising a combination of at least one inhibitor of the effect of a substance negatively effecting an immune response and at least one stimulator positively effecting an immune response. The substances negatively effecting an immune response

are selected from the Markush group comprising the targets TGF-beta, VEGF, interleukin 10, PGE2 and their respective receptors. A Markush group is a common tool to describe a related group in patents. The common effect of inhibiting one or more of these substances is to antagonize their negative effect on the immune system. In other words, the suppression of the immune system caused by each of these substances is lifted.

This common inhibiting effect can be reached by inhibiting the activating cascade of those substances in different ways, which is referred to in claims 2-6. One way is the inhibition of the synthesis of targets such as TGF-beta, VEGF, interleukin 10, PGE2 and their respective receptors by antisense oligonucleotides (claim 4). Antisense oligonucleotides hybridize with the m-RNA of their specific target and, thus, inhibit the formation of those targets. The same effect can be achieved by using specific ribozymes, which are oligonucleotides as well (claim 4).

Another way of inhibiting the signal pathway of molecules negatively effecting the immune system is achievable by binding a part of an antibody (Fab fragment or single chain antibody) to the above mentioned targets. A target molecule to which a part of an antibody is bound will not be able to activate its specific receptor and by this the down regulation of the immune system. In the same way, a receptor to which a part of an antibody is bound will no longer be available for its target molecule (e.g., TGF-beta, VEGF etc.). Also in this way, the down regulation of the immune system is blocked.

This illustrates that all substances mentioned in claims 1 to 6 have the common effect of blocking the signal pathways of substances negatively effecting the immune response. This common

effect allows, according to MPEP § 806.04 and MPEP § 808.01, combining these substances in one single application. Therefore, the inventions I and II, respectively II and IV, according to the proposal of the USPTO, are consistent. Inventions I and III, respectively II and IV, representing the treatment of an infectious disease and a neoplasm, are consistent as well.

That is, the immune system plays a key role in the inventions I/II and III/IV disease groups. Even if therapeutic treatment reduces bacteria, viruses, and parasites causing infectious diseases, the immune system has to finalize this treatment by eradicating the infectious agent, completely.

In the same way, in cancer therapy a lot of tumor cells are destroyed, e.g., by radiation or chemotherapy. Nevertheless, the remaining part of the tumor cells has to be eradicated by the immune system, itself.

This eradicating effect is only possible if the immune system works on a high (normal) level, which is not the case if the immune system is compromised by an immuno-suppressor, as mentioned in claim 1. At the same time, the immuno-suppressor is a very specific linking element for the treatment of infectious diseases and neoplasms.

Bacteria and virus as well as tumor cells can adversely effect the immune response by special escape mechanisms, e.g., they specifically suppress the immune system by over expressing a factor negatively regulating the immune system (e.g., TGF-beta). Therefore, enhancing the immune system by inhibiting the immuno-suppressors, and combining this effect with the effect of substances stimulating the immune system, will result to treatment of infectious diseases and neoplasms.

In conclusion, inventions I to IV are not properly restricted, but are based on a unified concept.

Applicant submits that restriction of invention V appears based on a misunderstanding of claim 9. Claim 9 defines a medicament comprising two or more of the inhibitors and/or two or more of the stimulators of claim 1. This claim uses the expression "at least one," which is used in claim 1 for both the stimulators and the inhibitors. Therefore claim 9 is not properly restricted from claim 1.

Traverse is also maintained in that no reasoning is provided for requiring election from among elements of claim 1 and claim 8.

Favorable action is requested.

Respectfully submitted,

JACOBSON HOLMAN PLLC

By: _____
William E. Player
Reg. No. 31,409

The Jenifer Building
400 Seventh Street, N.W.
Washington, D.C. 20004-2201
Tel.: 202-638-6666
Fax: 202-3935350
Date: May 5, 2004
WEP/bap
R:\rthomas\2004\APRIL\P66141US0 res.wpd

Attorney Docket No. P66141US0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: SCHLINGENSIEPEN et al.

Application No.: 09/701,583 Group Art Unit: 1635

Filed: February 5, 2001 Examiner: J. ZARA

For: A METHOD FOR STIMULATING THE IMMUNE SYSTEM

AMENDMENT

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The instant paper responds to the Office Action April 4, 2005.

Amendments to the claims begin on page 2 of this paper.

Remarks/Arguments begin on page 5 of this paper.

Amendments to the claims:

This listing of claims replaces all prior versions, and listings, of claims in the application.

Listing of claims:

1 (currently amended): A medicament for treating neoplasms comprising a combination of:

- at least one inhibitor of the effect of a substance negatively effecting an immune response, ~~the substance selected from the group consisting of TGF-β and its receptors, VEGF and its receptors, interleukin 10 (IL-10) and its receptors, PGE_2 and its receptors, wherein the inhibitor has a molecular weight of less than 100 kDa~~ wherein the inhibitor is an oligonucleotide having a sequence according to one of SEQ ID NOS: 1-213, unmodified or having one or more modifications selected from the group consisting of phosphorothioate internucleotide linkages, methylphosphonate internucleotide linkages, phosphoramidate linkages, peptide linkages, 2'-O-modified sugar, and modified bases and
- at least one stimulator positively effecting an immune response.

2 (previously presented): The medicament of claim 1 wherein the inhibitor is inhibiting the synthesis or function of molecules suppressing or downregulating or negatively affecting the immune response.

Claims 3-5 (cancelled).

6 (withdrawn): The medicament according to claim 1, wherein the inhibitor is a fab-fragment or single chain antibody (scFv).

7 (previously presented): The medicament according to claim 1, wherein the stimulator is enhancing the synthesis or function of molecules stimulating, enhancing, upregulating and/or positively regulating the immune response.

8 (previously presented): The medicament according to claim 7, wherein the stimulator is stimulating and/or enhancing the synthesis and/or the function of factors selected from the group consisting of GM-CSF, SCF, CSF, IFN, FLT-3-ligand, monocyte chemotatic proteins (MCP-1), interleukin-2, interleukin-4, interleukin-12 and/or interleukin-18 or the stimulator is one of the mentioned interluekins or is selected from the groups consisting of viruses, viral antigens, antigens expressed in tumor cells or pathogens, but not in normal cells, organ specific antigens expressed in affected organs which are not essential for the organism or fusion cell of dendritic and tumor cells.

9 (previously presented): The medicament according to claim 1, wherein the medicament comprises two or more of the inhibitors and/or the stimulators.

10 (currently amended): An oligonucleotide having ~~one of the sequences~~ a sequence according to one of SEQ ID NOS: 1-213, unmodified or having one or modifications selected from the group consisting of phosphorothioate internucleotide linkages, methylphosphonate internucleotide linkages, phosphoramidate linkages, peptide linkages, 2'-O-modified sugar, and modified bases.

11 (previously presented): The oligonucleotide according to claim 10 wherein each oligonucleotide is effective against expression of at least two of TGF-β_1, TGF-β_2 and/or TGF-β_3.

Claims 12 and 13 (cancelled).

Remarks/Arguments:

Applicants wish to thank Examiner Jane J. Zara for acknowledging receipt of the certified copy of the priority document and, accordingly, for granting foreign priority under 35 USC 119.

Claims 1 and 10, currently amended, and claims 2-4, 6-9, and 11, previously presented, are pending.

Claims 5, 12, and 13 are canceled, without prejudice or disclaimer.

Claim 6 is withdrawn, pursuant to restriction.

Claims 1 is amended, hereby, in order to incorporate claims 3-5. Claims 1 and 10 are amended, hereby, and in order to more clearly define the invention as described in the specification (page 8, ¶3)—to clarify that the oligonucleotide can have one or more modifications that are conventional in oligonucleotide chemistry—see, for example, Eurogentec, online at ** (a copy of which is attached, hereto, for the examiner's convenience). Claim 10 is, also, amended to more clearly define the instant invention—by using the identical language of the antecedent basis found in amended claim 1.

Claims 1-4, 7, 8, 12, and 13 were rejected under 35 USC 102(b) as being allegedly anticipated by *PNAS, 93*, 1996, 2909-2914 (Fakhrai). Reconsideration of the rejection is requested.

First of all, as applied against claims 4, 12, and 13 the rejection is rendered moot, since claims 4, 12, and 13 are cancelled, hereby.

Secondly, by the instant amendment, applicants have limited the (pending) rejected claims, *i.a.*, to the subject matter of claim 5. Since claim 5 was not rejected based on Fakhrai, the instant

amendment effectively renders the rejection moot. As such, withdrawal of the rejection under §102(b) based on Fakhrai appears to be in order.

Claims 1-4, 7, 8, and 9 were rejected under 35 USC 102(e) based on US 6,376,199 (Caniggia). Reconsideration is requested.

First of all, as applied against claims 4, the rejection is rendered moot, since claim is cancelled, hereby.

Secondly, as explained in the previously filed amendment, Caniggia is not available as prior art against the subject application under §102(e). The §102(e) date of the reference is December 21, 1999, which is antedated by the filing date of the subject, National Stage application—June 10, 1999.

Nevertheless, in order to advance prosecution, applicants have limited the rejected claims, hereby, to the subject matter of claim 5. Since claim 5 was not rejected based on Caniggia, the instant amendment effectively renders the rejection moot. As such, withdrawal of the rejection under §102(e) based on Caniggia appears to be in order.

The objection to claim 8 cannot be understood. According to the objection, "interleukins"—appearing at line 5 of the claim—is allegedly a "misspelling" (Office Action, page 4). The allegation appears to be incorrect. For the examiner's convenience, the cover page of United States Patent 5,919,898—entitled "Absorbent for Removing Interleukins and Tumor Necrosis Factor, and Process for Removing the Same" (emphasis added)— is attached hereto.

Claims 1-5 and 7-11 were rejected under 35 USC 112, 1st ¶, for allegedly failing to comply with the written description requirement. Reconsideration of the rejection is requested.

First of all, as applied against claims 4, 5, and 11, the rejection is rendered moot, since claims 4, 5, and 11 are cancelled, hereby.

Secondly, the statement of rejection alleges that the subject application does not provide sufficient descriptive support for the genera "inhibitor of the effect of a substance negatively effecting an immune response" and "stimulator positively effecting an immune response." In accordance with the instant amendment, the "inhibitor" genus is, now, limited to one of the oligonucleotides "of SEQ ID NOS: 1-213," optionally having one or more modifications that are conventional in oligonucleotide chemistry (as explained, above). Thus, the genus of "at least one inhibitor of the effect of a substance negatively effecting an immune response," as recited in the present (amended) claims, literally covers only the 213 oligonucleotide species expressly disclosed in the subject application, and those modifications, thereof, disclosed in the subject application, which are conventional in oligonucleotide chemistry. One of ordinary skill in the art would have, accordingly, readily appreciated all of the species that fall within the "inhibitor" genus "oligonucleotide" of the presently claimed invention (claims 10 and 11) and the oligonucleotide component of the presently claimed medicament (claims 1, 2, 7, 8, and 9).

With respect to the "stimulator" genus (component) of the presently claimed medicament, the present specification dedicates three complete pages (pages 3-5) to describing species within the claimed genus. While the statement of rejection (Office Action, page 6) alleges "One of skill in the

art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the . . . [inhibitor genus] claimed," it fails to explain *how* the three pages of text in the specification that are dedicated to describing species of the genus "fails to provide a representative number of species."

Moreover, medicament stimulators useful in accordance with the presently claimed invention include those well known in the art. Such well known stimulators need not be specifically identified in the subject application in order to satisfy the written description requirement of §112, ¶1. In order to satisfy the requirements of §112, first paragraph, "it is not necessary to embrace in the claims or describe in the specification all possible forms in which the claimed principle may be reduced to practice." *Smith v. Snow*, 294 U.S. 1, 11 (1935). The law does not require an applicant to describe in his specification every conceivable embodiment of the invention. *SRI Int'l v. Matsushita Elec. Corp. of America*, 227 USPQ 577, 586 (Fed. Cir. 1985).

For the foregoing reasons, both of the "inhibitor" and "stimulator" genera are supported by sufficient descriptive text in the present specification to satisfy the written description requirement of §112, ¶1. Accordingly, the rejection under §112, ¶1, for alleged failure to satisfy the written description requirement appears to be in order for withdrawal.

Claims 1-5 and 7-11 were rejected under 35 USC 112, 1st ¶, for allegedly lacking enablement. Reconsideration of the rejection is requested.

First of all, as applied against claims 4, 5, and 11, the rejection is rendered moot, since claims 4, 5, and 11 are cancelled, hereby.

Secondly, in order to sustain a rejection for lack of enablement, and shift the burden to a patent applicant, the PTO must cite evidence in support of any allegations of non-enablement, in addition to explaining *why* it doubts the truth of statements of enablement made in the specification. *In re Sichert*, 196 USPQ 209 (CCPA 1977). Lack of enablement is not demonstrated merely because the claim scope might, theoretically, cover embodiments that do not work; the function of the claims is not to specifically exclude possibly inoperative embodiments. *Atlas Powder v. E.I. du Pont de Nemours Co.*, 224 USPQ 409 (Fed. Cir. 1984). Even in an unpredictable area, such as chemistry, the PTO must advance reasons why a patent applicant's broad assertion of enablement is not true. *In re Bowen*, 181 USPQ 48 (CCPA 1974). Lack of enablement under §112 is not established by mere allegations of undue breadth, that is, by merely arguing that claims read on non-disclosed embodiments. *Horton v. Stevens*, 7 USPQ2d 1245 (BPA & I 1988). While working examples drawn to specific embodiments may be desirable, they are not *required* in order to satisfy enablement under §112. *In re Strahilevitz*, 212 USPQ 561 (CCPA 1982). It is well established that working examples are not necessary when one possessed of knowledge of ordinary skill in the art could practice the invention without the exercise of undue experimentation. *Ex parte Nardi*, 229 USPQ 79 (BPA & I 1986). "In satisfying the enablement requirement, an application need not teach, and preferably omits, that which is well known in the art." *Staehelin v. Secher*, 24 USPQ2d 1513, 1516 (BPA & I 1992).

As an initial matter, it must be remembered that the claims at issue define a composition of matter—a "medicament" (claims 1, 2, and 6-9) and the "oligonucleotide" component of the

medicament, itself (claim 10). Accordingly, while the "medicament" and the "oligonucleotide" are useful in the treatment of neoplasms, the claims at issue are not *treatment*, i.e., method, claims.

According to the statement of rejection, the rejection is based, *i.a.*, on the allegation "Applicants have not provided guidance in the specification toward a method of treating *any* neoplasm" (Office Action, page 9, *emphasis added*). In other words, satisfaction of enablement under §112, ¶1, (according to the statement of rejection) that the present specification must enable the treatment of *any* neoplasm. In this respect, the statement of rejection is mistaken.

Enablement under §112, ¶1, is satisfied for using the claimed invention when the "claimed invention meets at least one . . . objective" stated in the specification. *Carl Zeiss Stiftung v. Renishaw PLC*, 20 USPQ2d 1094, 1100 (Fed. Cir. 1991). "An invention . . . need only be useful to some extent and in certain applications." *Id.* Total incapacity, i.e., incapacity with respect to all uses of the invention described in the specification, is necessary to demonstrate lack of enablement with respect to the invention claimed. *Tol-O-Matic Inc. v. Proma Produkt-Und Marketing Gesellschaft m.b.H.*, 20 USPQ2d 1332, 1338 (Fed. Cir. 1991).

The statement of rejection admits that enablement is satisfied for at least one stated objective—"for treating a brain neoplasia" (Office Action, page 7). Accordingly, the statement of rejection implicitly acknowledges that enablement is satisfied for the presently claimed invention. *Carl Zeiss Stiftung, supra.* Withdrawal of the rejection under §112, ¶1, for alleged lack of enablement, appears to be in order.

Claims 1-5, 7, 8, 10, and 11 were rejected under 35 USC 102(a) as being allegedly anticipated by WO98/33904. Reconsideration of the rejection is requested.

First of all, as applied against claims 4, 5, and 11, the rejection is rendered moot, since claims 4, 5, and 11 are cancelled, hereby.

Secondly, WO98/33904 has an effective date as prior art, under §102(a), of 6 August 1998—its publication date. The rejected claims are entitled to a priority date under §119(a) no later than 25 July 1998, i.e., the filing date of EP98113974.4. Since WO98/33904 does not have an effective date as prior art before the priority date for the rejected claims, the rejection cannot be maintained. Withdrawal of the rejection under §102(a) based on WO98/33904 appears to be in order.

Claims 1-5, 7, 8, 10, and 11 were provisionally rejected under 35 USC 101 as allegedly claiming the same invention as claims 12-15 in US10/984,919. Reconsideration of the rejection is requested.

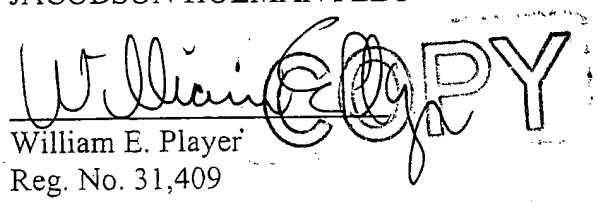
First of all, as applied against claims 4, 5, and 11, the rejection is rendered moot, since claims 4, 5, and 11 are cancelled, hereby.

Secondly, the rejection is provisional. It only applies if and when claims 12-15—in the form relied on to support the rejection—are patented. Accordingly, the rejection is premature, since the claims relied on might never issue in a patent. Until the rejection is no longer provisional, no further reply is necessary.

Favorable action is requested.

Respectfully submitted,

JACOBSON HOLMAN PLLC

By 

William E. Player
Reg. No. 31,409

400 Seventh Street, NW
The Jenifer Building
Washington, D.C. 20004
Tel. (202) 638-6666
Fax (202) 393-5350
Date: October 4, 2005
WEP/kjp
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- Introduction
- Resistance towards nucleases
- Ability to cross the cell membrane
- Binding affinity and specificity
- Phosphorothioates
- Methylphosphonates
- 2'-O-Me Modified oligoribonucleotides
- C5-propyne and methyl analogs of dC and dT
- Chimeric oligos
- Antisense oligos Design Service

Introduction

With more than 15 years experience in the field of antisense research, Eurogentec has acquired the expertise to advice and to provide you with the best antisense chemistry designed for your specific experiments.

Antisense oligodeoxynucleotides (ODNs) must be designed with the following properties necessary for optimal activity:

ODNs must be nuclease resistant before and during residence in cells.
ODNs must have the ability to cross the cellular membrane with some level of efficiency.
ODNs must demonstrate high binding affinity and specificity for the target sequence.

In these terms, the most successfully used antisense oligonucleotides are:

- Phosphorothioates
- Methylphosphonates
- 2'-O-Me Modified oligoribonucleotides
- 5-propyne derivatives
- C5-methyl pyrimidine derivatives
- Chimeric oligos

Top

Resistance towards nucleases

Nuclease resistance is fairly easy to achieve by :

- Modification of the normal phosphodiester backbone (e.g., phosphorothioates, methylphosphonates)
- The incorporation of 2'-OMe-nucleotides (2'-OMe-RNA)
- The use of Peptide Nucleic Acids (PNA)
- The use of Locked Nucleic Acids (LNA)
- The use of a 3'-terminal cap (e.g., 3'-aminopropyl modification or by using a 3'-3' terminal linkage)

Top

Ability to cross the cell membrane

Transport of oligonucleotides into cells is a problem routinely faced by antisense researchers. Improved transport through the cellular membrane can be achieved by :

- The use of a carrier molecule linked to the antisense oligonucleotide (e.g., cholesterol)
- The use of tranfection reagents (Cytofectine, DAC 30, poly-imine...)
- Backbone modification to more lipophilic linkages (methylphosphonate)
- The incorporation of modified monomers (5-(1-propynyl)-2'-deoxy-Uridine (pdU) and 5-(1-propynyl)-2'-deoxyCytidine (pdC)

Top

Binding affinity and specificity

Increasing the affinity and specificity of an oligonucleotide has been more difficult to achieve since this necessitates modifying the natural bases which are already almost perfectly set up for optimal hydrogen bonding. To achieve this, it has been described that the recommended modifications are:

- Oligonucleotides containing 2'-OMe-nucleotides (2'-OMe-RNA) forms more stable hybrids with complementary RNA strands than equivalent DNA and RNA sequences
- Phosphorothioate linkages confer to the oligonucleotides a higher binding affinity
- C-5 methylated pyrimidine deoxy-nucleosides are known to form more stable duplexes and triplexes than their corresponding pyrimidine derivatives
- 5-(1-propynyl)-2'-deoxy-Uridine (pdU) and 5-(1-propynyl)-2'-deoxyCytidine (pdC) monomers demonstrated that both substitutions enhanced duplex stability

Top

Chimeric oligos

These kinds of oligos are now extensively analysed for at least three reasons:

- Oligos have some drawbacks (toxicity, non specific effects)
- Full or 2' O-Alkyl oligos do not induce RNase H
- Modifications like methylphosphonates or 2'O-Alkyl may increase the manufacturing costs

The presence of methylphosphonates or 2' O-Alkyl modification increases the affinity of the oligo for it's target RNA, and thus reduce the IC50. These modification also increase the nuclease resistance of the modified oligos, and have been shown to display lower drawbacks. This is also increased when C5-propynyl bases are introduced in the sequence. Therefore, the combination of various internucleotide linkages variants and C5-analogs is thus a very nice combination of all prerequisite for "good" antisense candidate.

Top

Antisense oligos Design Service

Eurogentec has initiated a collaboration with ExpressOn Biosystems Ltd. to provide its customers with the best design service and products ever in the antisense field.

Eurogentec offers ExpressOn antisense design service employing ACCESSarray 4000, cell-free assays, tissue culture, bioinformatics and gene expression profiling technology to give researchers the widest choice of design options. Three levels of service are provided to address the needs of all customers, whether Academic, Biotechnology and Pharmaceutical:

Eurogentec synthesizes all possible chemistries to provide the most appropriate oligos for your experiments. All commercially available scales, purifications, modifications and identification methods are offered. Please contact us for more information on these aspects.

Types of service
In addition to antisense design, reagents can be supplied ready calibrated and validated for specificity of knockdown. You choose the service that meets your needs.

Design of antisense
ACCESSarray 4000-based structure mapping of mRNA, data processing and analysis, design of up to five antisense oligos.

Calibration of knockdown level
Design service + quantification of knockdown in cell culture by qPCR (currently only gene expressed in HeLa cells, please contact us to discuss this service in other model systems).

Validation of Specificity
Design and calibration service + MicroArray-based gene expression profiling pre- and post-knockdown to determine non-target effects.

How does it work ?

You send us...
- A cDNA clone of your target gene
- The gene sequence or accession number

We perform...
- A transcription of your clone
- The hybridization of the RNA on the ACCESSarray to map its structure
- The analysis of the results using our ACCESSmapper software.

You get back...
- A complete ACCESSmap of your target gene
- A copy of the ACEESmaper software (see below for example data)
- 5 designs (further reagents can be readily designed using the data provided)

More information...
For more details or pricing information please send an e-mail to info@eurogentec.com.

Back

US005919898A

United States Patent [19]

Nakatani et al.

[11] Patent Number: 5,919,898

[45] Date of Patent: Jul. 6, 1999

[54] ABSORBENT FOR REMOVING INTERLEUKINS AND TUMOR NECROSIS FACTOR, AND PROCESS FOR REMOVING THE SAME

[75] Inventors: Masaru Nakatani; Shigeo Furuyoshi; Satoshi Takata, all of Kobe, Japan

[73] Assignee: Kanegafuchi Kagaku Kogyo Kabushiki Kaisha, Osaka, Japan

[21] Appl. No.: 08/590,599

[22] Filed: Jan. 24, 1996

[30] Foreign Application Priority Data

Jan. 27, 1995	[JP]	Japan	7-012082
Mar. 24, 1995	[JP]	Japan	7-066565
Mar. 30, 1995	[JP]	Japan	7-061182

[51] Int. Cl.[6] A61K 38/00

[52] U.S. Cl. 530/345; 530/412; 530/351

[58] Field of Search 530/351, 345, 530/412

[56] References Cited

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Primary Examiner—Johann Richter
Assistant Examiner—Patrick R. Delaney
Attorney, Agent, or Firm—Armstrong, Westerman, Hattori, McLeland & Naughton

[57] ABSTRACT

An adsorbent for removing at least one interleukin selected from the group consisting of inerleukin-1, interleukin-2, interleukin-6 and interluekin-8 and/or TNF, which comprises a porous water-insolube carrier and a compound satisfying the value of log P of at least 2.50, in which P is a distribution coefficient in an octanol-water system and being immobilized onto the carrier, a process for removing the above IL(s) and/or TNF by the adsorbent and an adsorber comprising the adsorbent. According to the present invention, IL(s) and TNF in body fluid can be efficiently absorbed using the above-mentioned adsorbent.

5 Claims, 2 Drawing Sheets

Attorney Docket No. P66141US0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: SCHLINGENSIEPEN et al.

Via facsimile
571-273-8300

Application No.: 09/701,583 Group Art Unit: 1635

Filed: February 5, 2001 Examiner: J. ZARA

For: A METHOD FOR STIMULATING THE IMMUNE SYSTEM

RESPONSE
TO ELECTION/RESTRICTION REQUIREMENT

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Sir:

This paper, transmitted by facsimile, responds to the Office Action (election/restriction requirement) mailed January 4, 2006.

Pursuant to the election/restriction requirement applicants elect SEQ ID NO: 9 and SEQ ID NO: 14, as the two nucleotide sequences (in addition to previously elected SEQ ID NO: 7), with traverse. All remaining claims read on the elected species, and all elected species are directed against TGF-β2.

Applicants traverse since, under MPEP 2434, nucleotide sequences encoding the same protein are not considered to be independent and distinct and will be examined together. In the present case, SEQ ID NOS: 1-32 are antisense oligonucleotides corresponding to a single gene encoding a single protein, i.e., protein TGF-β. Accordingly, SEQ ID NOS: 1-32 are not independent and distinct from one another.

Favorable action is requested.

Respectfully submitted,

JACOBSON HOLMAN PLLC

400 Seventh Street, N.W.
Washington, D.C. 20004-2201
Tel.: 202-638-6666
Fax: 202-3935350
Date: January 31, 2006
WEP/id
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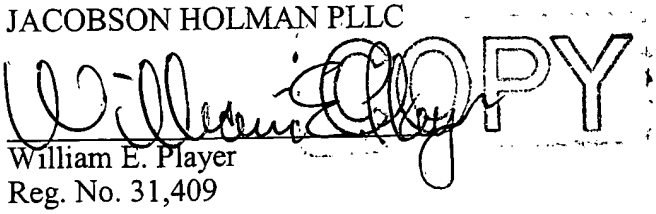
By: 

William E. Player
Reg. No. 31,409

Mat 4/24/04 WEP P66141US0

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TC 4-24-06

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/701,583	02/05/2001	Karl-Hermann Schlingensiepen	P66141US0	7033

136 7590 04/21/2006

JACOBSON HOLMAN PLLC
400 SEVENTH STREET N.W.
SUITE 600
WASHINGTON, DC 20004

JACOBSON HOLMAN PLLC
Response Due On Or Before
7 / 21 / 06
Month Day Year

EXAMINER	
ZARA, JANE J	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 04/21/2006

COPY

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/701,583	Applicant(s) SCHLINGENSIEPEN ET AL.
	Examiner Jane Zara	Art Unit 1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 6-11* is/are pending in the application.

4a) Of the above claim(s) *6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 7-11* is/are rejected.

7)☒ Claim(s) *8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11-02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 1-31-06.

Claims 1, 2, 6-11 are pending in the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

Applicant's additional election of SEQ ID Nos. 9 and 14 in the reply filed on 1-31-06 is acknowledged.

Claim 6 remains withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention as set forth in the prior Office action, there being no allowable generic or linking claim. SEQ ID Nos. 7, 9 and 14, and claims 1, 2, 7-11 have been examined on their merits as set forth below.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Objections/Rejections

Claim Objections

Claim 8 is objected to because of the following informalities: in line 5, **"interluekins"** is a misspelling. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2 and 7-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record set forth in the Office action mailed 4-4-05.

The claims are drawn to a pharmaceutical composition comprising at least one oligonucleotide inhibitor of an immune response selected from SEQ ID Nos. 1-213, and further comprising at least one stimulator positively effecting an immune response, which stimulator enhances the synthesis and/or function of factors selected from GM-CSF, SCF, CSF, IFN, FLT-3-ligand, monocyte chemotactic proteins, IL-2, IL-4, Il-12 and/or IL-18, a virus, viral antigen, tumor or pathogenic antigen, or organ specific antigens expressed in affected organs but not essential for the organism or fusion of dendritic and tumor cells.

Applicant's arguments filed 10-4-05 have been fully considered but they are not persuasive. Applicant argues that adequate written description has been provided for the very broad genus comprising the above mentioned stimulators positively effecting an immune response because the specification dedicates three pages to describe the immuno-stimulating compounds. Applicant argues further that, in order to satisfy the written description requirement, Applicant is not required to embrace in the claims, or describe in the specification, all possible forms in which the claimed principle may be

reduced to practice. Applicants are correct that a laundry list of immuno-stimulating compounds have been provided on pages 3-5 of the instant specification. The recitation of a laundry list of members of this very broad genus, however, does not provide adequate description for the claimed genus which encompasses, but is not limited to a very broad array of molecules and biological agents, including but not limited to *GM-CSF, SCF, CSF, IFN, FLT-3-ligands, monocyte chemotactic proteins, IL-2, IL-4, Il-12 and/or IL-18, any virus or viral antigens, any tumor or pathogenic antigens, and any organ specific antigens expressed in affected organs but not essential for the organism or fusion of dendritic and tumor cells*, which composition provides for treatment effects, as embraced by the claimed term "medicament." Applicants have not provided any treatment effects for a representative number of species of the broad genus claimed, which are used in combination with the negative effector oligonucleotides. the claimed genus embraces a myriad of biological agents as medicaments, none of which are shown in the instant disclosure to provide for the function claimed that of providing treatment effects in an organism. For these reasons, the instant written description rejection is maintained.

Claims 1, 2 and 7-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vitro inhibition of TGF-β expression comprising the administration of antisense oligonucleotides does not reasonably provide enablement for the targeting and inhibition of the TGF-β family in vivo using any antisense or optionally in combination with a tumor cell extract, and which provides for

treatment effects in an organism for the reasons of record set forth in the Office action mailed 4-4-05.

The claims are drawn to therapeutic (pharmaceutical) compositions for treating a neoplasm comprising the administration of a medicament comprising an antisense oligonucleotide of SEQ ID NO: 7, 9, or 14, and further comprising at least one stimulator positively effecting an immune response, which stimulator enhances the synthesis and/or function of factors selected from GM-CSF, SCF, CSF, IFN, FLT-3-ligand, monocyte chemotactic proteins, IL-2, IL-4, Il-12 and/or IL-18, a virus, viral antigen, tumor or pathogenic antigen, or organ specific antigens expressed in affected organs but not essential for the organism or fusion of dendritic and tumor cells.

Applicant's arguments filed 10-4-05 have been fully considered but they are not persuasive. Applicant argues that enablement is satisfied for the entire scope of the presently claimed invention because Fakrai et al (Proc. Natl. Acad. Sci. 93: 2909-2914, 1996) disclose the treatment of tumors in mice following administration of a TGF-beta antisense vector. Contrary to Applicant's assertions, the enablement of Fakrei et al to provide treatment effects in tumor bearing mice by administering a TGF-beta antisense vector does not provide enablement for the instantly claimed invention. The ability of one molecule to provide treatment effects in an animal model does not enable another molecule to do the same, In vivo efficacy is not predictable and it requires undue experimentation beyond that provided in the instant disclosure for the broad array of medicaments claimed. In vitro data provided in the specification is not extrapolatable to in vivo efficacy. The antisense claimed in the instant invention were shown to provide

target gene inhibition in vitro, but not in vivo - alone, or in combination with any member of the very broad genus of immuno-stimulatory compounds claimed. For these reasons, the enablement rejection is maintained.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1, 2, 7, 8, 10 and 11 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 12-15 of copending Application No. 10/984,919. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented. Both sets of claims are drawn to pharmaceutical compositions comprising at least one inhibitor of an immune suppressor (e.g. antisense targeting and inhibiting the expression of TGF-β or its receptors) and one immune stimulator (*see* accompanying sequence alignment data of SEQ ID NOs: 528 and 532 of 10/984,919 and SEQ ID NOs. 7 and 14 respectively of the instant application: They are the same oligonucleotides).

Claims 1, 2, 7, 8, 10 and 11 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1 and 6 of copending Application No. 10/220,033. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented. Both sets of claims are drawn to pharmaceutical compositions comprising at least one inhibitor of an immune suppressor (e.g. antisense targeting and inhibiting the expression of TGF-β or its receptors) and one immune stimulator (*see* accompanying sequence alignment data of SEQ ID NO: 5 of 10/220,033 and SEQ ID NO. 14 of the instant application: They are the same oligonucleotide).

New Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 7, 8, 10 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Schlingensiepen et al (WO 94/25588).

Schlingensiepen et al teach pharmaceutical compositions comprising at least one inhibitor of an antisense oligonucleotide of SEQ ID NO: 9, which targets and inhibits the expression of TGF-β or its receptors and one immune stimulator (see the abstract, fig. 8, pages 14, 22, 23, and the accompanying sequence alignment data between SEQ ID NO: 72 of WO 94/25588 and SEQ ID NO: 9 or the instant application).

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 10 and 11 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-3 of prior U.S. Patent No. 6,455,689. This is a double patenting rejection.

Schlingensiepen et al (USPN 6,455,689) teach the oligonucleotide of SEQ ID No. 9 for targeting and inhibiting TGF-β (See the accompanying sequence alignment data of SEQ ID NO. 72 of 6,455,689 and SEQ ID NO. 9 of the instant application).

Conclusion

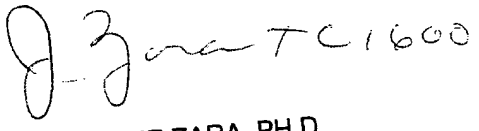
Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. 1.6(d)). The official fax telephone number for the Group is **571-273-8300**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO

DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (571) 272-0811. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
4-8-06



JANE ZARA, PH.D.
PRIMARY EXAMINER

Attorney Docket No. P66141US0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of SCHLINGENSIEPEN et al.

Application No.: 09/701,583 Art Unit: 1635

Filed: February 5, 2001 Examiner: Jane J. Zara

For A METHOD FOR STIMULATING THE IMMUNE SYSTEM

AMENDMENT AND
REQUEST TO RECONSIDER
FINAL RESTRICTION/ELECTION REQUIREMENT

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The instant paper responds to the Office Action mailed April 21, 2006.

Amendments to the claims begin on page 2 of this paper.

Remarks/Arguments begin on page 6 of this paper.

Amendments to the claims:

This listing of claims replaces all prior versions, and listings, of claims in the application.

Listing of claims:

1 (currently amended): A ~~medicament for treating neoplasms~~ composition comprising a physiologically acceptable combination of:

- at least one inhibitor of the effect of a substance negatively effecting an immune response, wherein the inhibitor is an oligonucleotide having a sequence according to one of SEQ ID NOS: 1-213, unmodified or having one or more modifications selected from the group consisting of phosphorothioate internucleotide linkages, methylphosphonate internucleotide linkages, phosphoramidate linkages, peptide linkages, 2'-O-modified sugar, and modified bases and
- at least one stimulator positively effecting an immune response.

2 (currently amended): The ~~medicament~~ composition of claim 1 wherein the inhibitor is inhibiting the synthesis or function of molecules suppressing or downregulating or negatively affecting the immune response.

Claims 3-5 (cancelled).

6 (withdrawn): The ~~medicament~~ composition according to claim 1, wherein the inhibitor is a fab-fragment or single chain antibody (scFv).

7 (currently amended): The ~~medicament~~ composition according to claim 1, wherein the stimulator is enhancing the synthesis or function of molecules stimulating, enhancing, upregulating and/or positively regulating the immune response.

8 (currently amended): The ~~medicament~~ composition according to claim 7, wherein the stimulator is stimulating and/or enhancing the synthesis and/or the function of factors selected from the group consisting of GM-CSF, SCF, CSF, IFN, FLT-3-ligand, monocyte chemotatic proteins (MCP-1), interleukin-2, interleukin-4, interleukin-12 and/or interleukin-18 or the stimulator is one of the mentioned ~~interluckins~~ interleukins or is selected from the groups consisting of viruses, viral antigens, antigens expressed in tumor cells or pathogens, but not in normal cells, organ specific antigens expressed in affected organs which are not essential for the organism or fusion cell of dendritic and tumor cells.

9 (currently amended): The ~~medicament~~ composition according to claim 1, wherein the ~~medicament~~ composition comprises two or more of the inhibitors and/or the stimulators.

10 (currently amended): An oligonucleotide having a sequence according to one of SEQ ID NOS: 1-213, excluding SEQ ID NOS: 1, 4, 5, 9, 11-13, 15-18, 20, 22, 23, and 25-27, unmodified or having one or modifications selected from the group consisting of phosphorothioate internucleotide linkages, methylphosphonate internucleotide linkages, phosphoramidate linkages, peptide linkages, 2'-O-modified sugar, and modified bases.

11 (previously presented): The oligonucleotide according to claim 10 wherein each oligonucleotide is effective against expression of at least two of TGF-β_1, TGF-β_2 and/or TGF-β_3.

Claims 12 and 13 (cancelled).

Remarks/Arguments:

Applicants wish to thank the examiner for the careful attention given the Rules in making the instant action non-final.

Claims 1, 2, and 6-10, currently amended, and claim 11, previously presented, are pending.

Claims 3-5, 12, and 13 are canceled, without prejudice or disclaimer.

Claim 6 is withdrawn, pursuant to restriction.

Examination was limited to SEQ ID NOS: 7, 9, and 14 pursuant to election/restriction, made final in the Office Action. Reconsideration of the final election/restriction requirement is requested, as set forth below.

Claims 1-9 are amended by changing the "medicament for treating neoplasms comprising a combination of" to a "composition comprising a physiologically acceptable combination of."

Claim 8 is amended to correct a misspelling.

Claim 10 and claim 11 (being dependent on claim 10) are amended by adding the proviso "excluding SEQ ID NOS: 1, 4, 5, 9, 11-13, 15-18, 20, 22, 23, and 25-27." The proviso is added in connection with the §101 rejection, discussed below.

The objection to claim 8 is overcome by amending the claim to correctly spell "interleukins."

Claims 1, 2, and 7-9 were rejected under 35 USC 112, first paragraph, as allegedly failing to comply with the written description requirement. Reconsideration is requested.

First of all, the rejection is not for the same reasons set forth in the previous Office Action, as maintained in the statement of rejection. According to the reasoning set forth in the prior

rejection, "the disclosure fails to provide a representative number of species to describe the various genara claimed" (Office Action mailed April 4, 2005, page 6, last three lines). This reasoning is not used as the basis of the present rejection (nor is it repeated).

According to the present statement of rejection the written description requirement is not satisfied because the rejected claims allegedly encompass

treatment effects, as embraced by the claimed term "medicament."

In other words, the rejection relies on the term "medicament" appearing in the claims, otherwise, the "treatment effects"—the alleged lack of which being the missing written description necessary to satisfy §112, ¶1—would not be an inherent feature of the claims, according to the statement of rejection.

Contrary to the rejected claims, the present claims do not recite the term "medicament" and, so, do not inherently embrace the "treatment effects," inherently embraced by the term "medicament." Since the "treatment effects" are not embraced by the present claims, the rejection is no longer supported, i.e., the statement of rejection fails to identify any subject matter presently claimed for which the specification fails to satisfy the written description requirement of §112, ¶1. Withdrawal of the rejection appears to be in order.

Claims 1, 2, and 7-9 were rejected under 35 USC 112, first paragraph, for allegedly lacking enablement. Reconsideration is requested.

First of all, with all due respect, the statement of rejection does not answer the arguments traversing the rejection set forth in applicant's amendment filed October 4, 2005. The statement of

rejection mistook the arguments traversing the written description rejection for the arguments traversing the enablement rejection, repeated as follows.

> According to the statement of rejection, the rejection is based, *i.a.*, on the allegation "Applicants have not provided guidance in the specification toward a method of treating *any* neoplasm" (Office Action, page 9, *emphasis added*). In other words, satisfaction of enablement under §112, ¶1, (according to the statement of rejection) that the present specification must enable the treatment of *any* neoplasm. In this respect, the statement of rejection is mistaken.
>
> Enablement under §112, ¶1, is satisfied for using the claimed invention when the "claimed invention meets at least one . . . objective" stated in the specification. *Carl Zeiss Stiftung v. Renishaw PLC*, 20 USPQ2d 1094, 1100 (Fed. Cir. 1991). "An invention . . . need only be useful to some extent and in certain applications." *Id.* Total incapacity, i.e., incapacity with respect to all uses of the invention described in the specification, is necessary to demonstrate lack of enablement with respect to the invention claimed. *Tol-O-Matic Inc. v. Proma Produkt-Und Marketing Gesellschaft m.b.H.*, 20 USPQ2d 1332, 1338 (Fed. Cir. 1991).
>
> The statement of rejection admits that enablement is satisfied for at least one stated objective—"for treating a brain neoplasia" (Office Action, page 7). Accordingly, the statement of rejection implicitly acknowledges that enablement is satisfied for the presently claimed invention. *Carl Zeiss Stiftung, supra.*

Furthermore, according to the statement of rejection (Office Action, page 4, last incomplete ¶), the specification is "enabling for in vitro inhibition of TGF-β." Thus, the statement of rejection admits that enablement is satisfied for at least one more stated objective (besides "for treating a brain neoplasia")—in vitro inhibition of TGF-β. Accordingly, the statement of rejection

(again) implicitly acknowledges that enablement is satisfied for the presently claimed invention. *Carl Zeiss Stiftung, supra.*

Further, still, it must be remembered that the present claims are not drawn to a medicament bu, rather, to a "composition." Any reasoning based on the term "medicament" appearing in the claims is, accordingly, no longer relevant. (Office Action, page 7).

For the foregoing reasons, withdrawal of the rejection under §112, ¶1, for alleged lack of enablement, appears to be in order.

Claims 1, 2, 7, 8, 10, and 11 were provisionally rejected under 35 USC 101 as allegedly claiming the same invention as claims 12-15 in US10/984,919. Reconsideration of the rejection is requested for the reasons of record.

The rejection is provisional. It only applies if and when claims 12-15—in the form relied on to support the rejection—are patented. Accordingly, the rejection is premature, since the claims relied on might never issue in a patent. Until the rejection is no longer provisional, no further reply is necessary.

Claims 1, 2, 7, 8, 10, and 11 were rejected under 35 USC 102(b) as being allegedly anticipated by WO94/25588 (Schlingensiepen). Reconsideration of the rejection is requested.

For anticipation under § 102 to exist, each and every claim limitation, as arranged in the claim, must be found in a single prior art reference. *Jamesbury Corp. v. Litton Industrial Products, Inc.*, 225 USPQ 253 (Fed. Cir. 1985). The "absence" from a prior art reference of a single claim limitation "negates anticipation." *Kolster Speedsteel A B v. Crucible Inc.*, 230 USPQ 81, 84 (Fed.

Cir. 1986). A reference that discloses "substantially the same invention" is not an anticipation. *Jamesbury Corp.* To anticipate the claim, each claim limitation must "*identically* appear" in the reference disclosure. *Gechter v. Davidson*, 43 USPQ2d 1030, 1032 (Fed. Cir. 1997) (*emphasis added*). To be novelty defeating, a reference must put the public in possession of the identical invention claimed. *In re Donahue*, 226 USPQ 619 (Fed. Cir. 1985).

Schlingensiepen does describe an antisense oligonucleotide corresponding to SEQ ID NO: 9. On the other hand, neither the Abstract, nor Figure 8, nor any of pages 14, 22, and 23 (nor, apparently, the entire disclosure) of the reference describes the component (limitation) "stimulator positively effecting an immune response" of the rejected "medicament" claims (and the present "composition claims"), allegations to the contrary in the statement of rejection, notwithstanding. As the reference fails to meet all limitations of the rejected (and present) claims.

Accordingly, the "absence" from Schlingensiepen of one of the limitations on the rejected (and present) claims "negates anticipation" by the reference. *Kolster Speedsteel A B*, 230 USPQ at 84. Withdrawal of the rejection under §102(b) appears to be in order.

Claims 10 and 11 were rejected under 35 USC 101 for allegedly claiming the same invention as claims 1-3 of US6455689. Reconsideration is requested.

In view of the proviso—"excluding SEQ ID NOS: 1, 4, 5, 9, 11 to 13, 15-18, 20, 22, 23, 25, 26, and 27"—limiting claims 10 and 11 (currently amended), none of the remaining recited sequences—non-excluded from "SEQ ID NOS: 1-213"—meets any of the sequences recited in each

of claims 1-3 in US6455689. Accordingly, the §101 rejection is overcome and, so, withdrawal of the rejection appears to be in order.

Request to Reconsider Final Restriction/Election Requirement

Moreover, with all due respect, even if MPEP 2434 were not violated, the restriction/election is, still, improper for requiring election of, and limiting examination to, only three (3) nucleotide sequences—contrary to the requirements of MPEP 803.04. In accordance with MPEP 803.04 ("Nucleotide Sequences") (emphasis added),

> "nucleotide sequences" . . . normally constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. . . . Nevertheless, . . . without creating an undue burden on the Office, the Director has decided sua sponte to . . . permit a reasonable number of such nucleotide sequences to be claimed in a single application. . . . [N]ormally ten sequences constitute a reasonable number for examination purposes. . . . Applications claiming more than ten . . . will be subject to a restriction requirement. Only the ten nucleotide sequences selected in response to the restriction requirement and any other claimed sequences which are patentably indistinct therefrom will be examined.

Contrary to the requirements of MPEP 803.04, the restriction/election incorrectly (1) required selection of only three nucleotide sequences, rather than the requisite "ten nucleotide sequences," and (2) restricted examination to the three elected nucleotide sequences, rather than "the ten nucleotide sequences . . . and any other claimed sequences which are patentably indistinct therefrom," as required.

The restriction/election violates the requirements of MPEP 2434, as pointed out in applicants' traverse, accompanying their election. Compliance with MPEP 2434 requires that SEQ ID NOS:

1-32 and 58-67—less those sequences expressly excluded by the claims—must be examined together, since they correspond to a single gene encoding the single protein TGF-β.

For the foregoing reasons, withdrawal of the final restriction/election requirement appears to be in order. Moreover, in the event a new (replacement) restriction/election requirement is made, it should be in compliance with MPEP 803.04—by providing for election of at least "ten nucleotide sequences" and by examining followed "the ten nucleotide sequences . . . and any other claimed sequences which are patentably indistinct therefrom."

Favorable action is requested.

Respectfully submitted,

JACOBSON HOLMAN PLLC

By 

William E. Player
Reg. No. 31,409

400 Seventh Street, NW
The Jenifer Building
Washington, D.C. 20004
Tel. (202) 638-6666
Fax (202) 393-5350
Date: September 21, 2006
WEP/jhr
R:\Home\rthomas\wep\2006\September\P66141US0 amdt.wpd